28. (Previously presented) The method of 26, wherein said noribogaine or its salt is administered to said patient at a dose of between 0.1 mg and 100 mg per kg of body weight

29. (Previously presented) The method of claim 27, wherein said noribogaine or its salt is administered at a dose of between 1.0 mg and 30 mg per kg of body weight.

30. (Currently amended) The method of claim ~~27~~ 28, wherein said noribogaine or its salt is administered at a dose of between 1.0 mg and 30 mg per kg of body weight.

Remarks

Claims 1-2, 4-5 and 25-30 are pending in the present application, claims 10-24 having been cancelled previously *without prejudice* pursuant to the Examiner's restriction requirement and Applicant's decision to elect with traverse to prosecute the invention of original claims 1-9. Upon the indication of allowable subject matter, and before the issuance of any patent from this application, Applicant will give consideration to filing a divisional application for the claimed subject matter cancelled in this paper. Applicant and her attorney wish to thank Examiner Jiang for taking the time from her busy schedule to conduct a telephonic interview with Applicant and her attorney during which the teachings of the cited prior art were discussed.

The Examiner has rejected the previously submitted claims 1-2, 4-5 and 25-30 as adding new matter to the amended claims, as well as being obvious over the teachings of the art of record. In addition, the Examiner objects to claims 27-28 and 29-30 as being duplicate claims. Applicant shall deal with each of these rejections/objections separately.

The Objection to Claims 27-28 and 29-30

The Examiner has objected to claims 27-28 and 29-30 as being duplicate claims. Applicants respectfully disagree. In each instance, the claims read on distinguishable methods, wherein the limitations in the claims are sufficiently different to comply with 37 C.F.R. 1.75. Note that claims 27 and 28 are dependent on different claims (25 and 26), each of which claims a method which is clearly distinguishable from the other. In addition, claims 29 and newly amended claim 30 are each dependent on different claims, which are clearly

distinguishable from each other. Consequently, Applicants have claimed the subject matter in the instant application in a manner which complies with the requirements of 37 C.F.R. §1.75. Applicant respectfully requests the Examiner withdraw her objection of claims 27-28 and 29-30 based upon the above discussion and the amendment to claim 30.

The New Matter Rejection

The Examiner has rejected the previously filed amended claims as having incorporated new matter. Essentially, the Examiner considers the insertion of the term "without addition" [sic] to constitute new matter. Applicant disagrees inasmuch as there is support for the term "without addiction" in the specification page 3, lines 3-4 ("noribogaine has been found to be useful as a non-addictive analgesic agent"), on page 8, lines 27-29 ("One of the main advantages of noribogaine is that it is not habit forming. Thus, pain relief can be accomplished without the risk of dependence associated with the chronic use of narcotics.") and on page 9, lines 21-22 ("noribogaine...has efficacy as an antinociceptive agent that can be used without the abuse liability inherent [to] opiates"). It is respectfully submitted that the term "without addiction" is fully supported by the originally filed specification.

The Obviousness Rejection

Separately, the Examiner maintains the rejection of previously submitted claims 1-9 under 35 U.S.C. §103 as being obvious over Epstein, et al., U.S. No. 3,715,361 ("Epstein") and GB 841,697 ("GB '697"), in view of Bagal, et al., ("Bagal") and Hussain, U.S. No. 4,464,378 ("Hussain"). The Examiner essentially argues that despite Applicant's arguments previously submitted, this was unconvincing because there is motivation to combine the references and the results obtained pursuant to the present application are expected. The Examiner relies on Epstein for putatively disclosing that ibogaine and its derivatives are analgesic agents and consequently, the agents are therefore useful in treating or alleviating pain. The Examiner relies on GB '697 for teaching that ibogaine is an analgesic agent and therefore is useful in an analgesic composition for treating or alleviating pain. The Examiner acknowledges that the prior art does not expressly disclose the employment of noribogaine alone or in combination with an opioid antagonist in a method of treating a patient to alleviate pain. The Examiner cites Bagal for disclosing that noribogaine is a known active metabolite of

ibogaine and that noribogaine enhanced morphine antinociception was more pronounced than with comparable ibogaine treatment. Finally, the Examiner cites Hussain for teaching that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient.

Given the teachings of the prior art, the Examiner contends that one of ordinary skill would have been motivated to employ noribogaine alone or in combination with an opioid antagonist such as naloxone, naltrexone or nalorphine in a method of treating a patient to alleviate pain and to optimize the effective amounts of agents in the composition herein to be administered. In particular, the Examiner cites and relies heavily on Bagal for teaching the instant invention for the reasons which are set forth in the office action. Applicant respectfully traverses the Examiner's rejection.

The present invention relates to the unexpected discovery that noribogaine, in contrast to ibogaine, may be used as a *non-addictive* analgesic agent (i.e., noribogaine can be used to treat pain in a patient without addiction), *alone* or in combination with an opioid *antagonist* as a particularly effective non-addictive analgesic. Without being limited by way of theory, it is believed that noribogaine functions, at least in part, as a full *mu* (μ) opioid receptor *agonist* without addictive properties. Consequently, the present invention makes use of noribogaine's unique activity and represents a particularly effective method for alleviating pain, an advance in the art and an exciting improvement over the treatments of the prior art. Methods which make use of noribogaine in combination with an opioid antagonist represent alternative embodiments of the present invention. Note that noribogaine is particularly effective as an analgesic agent because it is a full *mu* opioid agonist, is particularly effective in this regard, and is also *non-addictive*, in contrast to the opioid analgesics, i.e., the opioid agonists, such as morphine and related compounds. In addition, in contrast to ibogaine, noribogaine is vastly superior in analgesic activity (in fact, ibogaine is known in the art as possessing no significant analgesic activity on its own) and is free from the psychomimetic side effects of ibogaine.

In contrast to the Examiner's arguments, the present invention is clearly patentable and non-obvious over the teachings relied upon by the Examiner. The Examiner cites Epstein and GB '697, in view of Bagal and Hussain as rendering the present invention obvious. It is respectfully submitted by Applicant that Epstein and GB '697 do not teach or suggest the

present invention, that Hussain, by failing to even mention the present invention, does not obviate the deficiencies of Epstein and GB '697, and if one goes further and asserts Bagal against the present invention, the combination of references actually *teaches away* from the present invention. A detailed discussion of the patentability of the present invention follows.

It is clear from the art and even the Examiner's office action that none of the references teach noribogaine as an analgesic, either alone or in combination with an opioid *antagonist* as claimed. A review of Epstein shows that this reference does not even disclose noribogaine. Note that Epstein discloses a series of acyl derivatives of ibogaine for use as potential analgesic/anti-inflammatory analogs. Epstein does not disclose noribogaine, which is presented in the present specification on page 6. Epstein does not disclose ibogaine as an analgesic agent (indeed, it is not known in the art as an analgesic agent), but rather points to acyl derivatives of ibogaine as having analgesic and anti-inflammatory activity. Note here that the Examiner has contended that Epstein teaches ibogaine as an analgesic agent- *it does not.* Epstein is actually silent as to ibogaine's use as an analgesic agent and GB '697 clearly teaches that ibogaine does ***not*** possess analgesic activity itself (see page 2, first column, lines 5-9 of GB '697). Moreover, the mere assertion of activity does not evidence that the compounds would necessarily be used as pharmaceutical agents. In addition, in the chemical compounds which are disclosed by Epstein at columns 1 or 2 or otherwise described in Epstein, *noribogaine is not discussed or suggested.* In each analog which is disclosed by Epstein, the O-methyl group on the benzene ring of the molecule is always an O-methyl group. Epstein completely failed to appreciate the potential activity of noribogaine or that the O-methyl group is advantageously converted to a hydroxyl group to provide the activity of noribogaine. Because Epstein does not disclose noribogaine or the chemical conversion of the O-methyl group which may be advantageously employed in noribogaine to provide its activity, Epstein clearly does not disclose or suggest the present invention. There is no disclosure in Epstein that ibogaine is a useful stand-alone analgesic agent itself- indeed the entire rationale behind the approach of Epstein is to find a useful analgesic because ibogaine is not useful as an analgesic.

GB '697 Teaches That Ibogaine is Not An Analgesic per se

GB '697 describes the use of a number of narcotic morphine analogs (including

morphine) in combination with ibogaine or tabernanthine for analgesic use. GB '697 does not disclose noribogaine as an analgesic agent alone, and further only suggests the use of an addictive analgesic agent having morphine-like characteristics (i.e., an opioid analgesic) in combination with ibogaine or tabernanthine. This disclosure is actually duplicative in some measure with Bagal, discussed infra. In preferred embodiments of GB '697, as set forth in examples 1-2 5, 7-8 and 11, the use of morphine is described in combination with ibogaine or tabernanthine. This teaching is in complete contrast to the present invention inasmuch as the present invention relies on noribogaine as a *nonaddictive* analgesic acting *alone* in the first instance, and when combined with another agent, that agent is an opioid *antagonist*- i.e., an *opioid inhibitor*, not an opioid *agonist* such as morphine. A review of the instant claims shows that Applicant specifically has disclaimed any subject matter which might read on the teachings of GB '697. Note that the present methods are used in "the absence of an opioid analgesic", such as morphine or a related opioid agonist. Thus, GB '697 clearly does not teach the present invention, for it fails to teach or suggest noribogaine even obliquely, and when it discloses ibogaine, ibogaine is disclosed only *in combination* with another agent, that agent being the addictive analgesic agent morphine. ***Note that GB '695 clearly indicates at page 2, column 1, lines 5-6 that the art recognized that ibogaine per se did not have analgesic activity.*** GB '697 clearly does not obviate the deficiencies of Epstein in failing to disclose or suggest the present invention.

Turning to Hussain, this reference completely fails to even disclose or suggest noribogaine and consequently, fails to disclose or suggest the present invention. In the present invention, the use of noribogaine *alone or in combination* with an opioid antagonist to treat pain is claimed. The use of an opioid antagonist *only* in combination with noribogaine is claimed. None of Epstein, GB '697 or Hussain teaches that noribogaine may be used as an analgesic, alone or in combination with an opioid antagonist. Hussain in particular, merely provides certain known compounds adapted for nasal administration. It has relatively little relevance in bolstering the Examiner's arguments. However, note that the art does not recognize that opioid antagonists have analgesic activity, and it is respectfully submitted that opioid antagonists do not exhibit any significant analgesic activity. Moreover, Hussain does not even mention noribogaine or ibogaine. Consequently, none of these references alone or in combination teaches or suggests the present invention and the present invention is non-obvious over the disclosure of these references.

Turning to Bagal, it is respectfully submitted that this reference does not disclose or suggest the present invention of using noribogaine *alone or in combination with an opioid antagonist* as an effective analgesic agent. In the first instance, Bagal is prior art under 102(a), inasmuch as the Bagal paper published on November 25, 1996, a date which is less than a year after the provisional application from which the present application claims priority was filed.[1] Notwithstanding the question as to whether or not Bagal even is prior art, it is respectfully submitted that Bagal's teachings in combination with the other references do not render the present invention invalid. A review of the Bagal disclosure evidences that the teachings of this reference actually *teach away* from the present invention because this reference simply teaches that noribogaine, like ibogaine, may be used *in combination* with morphine, an opioid agonist. Bagal discloses the impact of ibogaine and noribogaine on other opiate actions. Bagal investigated the potentiation of ibogaine's effect on morphine analgesia. In particular, Bagal describes experiments which investigated the effects of ibogaine and noribogaine on morphine-induced antinociception. The experiments of Bagel clearly resulted in the finding that the co-administration of ibogaine and morphine resulted in an enhancement of morphine action which was dose dependent (see page 259 right column and 260, left column). This experiment merely confirmed the teachings of GB '697. Experiments involving noribogaine, which are described on pages 260-261, evidence that noribogaine exhibited *only slight albeit non-significant antinociceptive properties alone* and minimal effects on *morphine* antinociception when given 19 hours earlier (Bagal, page 261, top right column), but significant antinociceptive activity when co-administered with morphine. Thus, the teachings of Bagal show that noribogaine, like ibogaine, *may have* potentiated the analgesic effects of morphine within the test system employed.

[1] Although it is Applicant's view that Bagal does not impact the present invention or otherwise render the present invention invalid, either alone or in combination, Applicant reserves the right to make the appropriate showing to remove Bagal as a reference against the present application.

Bagal Does Not Teach the Use of Noribogaine Alone as an Analgesic Agent

In Bagal, contradictions to any conclusion of noribogaine's use as an analgesic agent *per se* come from:

1) Figure 1: Ibogaine has no effect on nociception when given alone- 19 hours prior. This is when noribogaine would likely be present- yet it has no effect; and

2) Figures 4 and 5: Looking at the plots of where noribogaine is given alone; although there is a trend toward an effect, it is deemed insignificant due to the similarity of both plots where noribogaine is given 19 hours prior and when noribogaine is given immediately. Clearly, the slight slope provided has nothing to do with the drug, but rather represents normal variance in experimental behavior data across test subjects.

Bagal concluded that noribogaine, when co-administered with morphine, simulated the results obtained with ibogaine-morphine co-administration. Thus, Bagal concluded that both ibogaine and noribogaine increased morphine antinociception when *co-administered with morphine*. Bagal also concluded that a 19 hour pretreatment with noribogaine showed only a slight ("if any") enhancement of morphine antinociception (p. 261, right column, bottom). **Bagal concluded that noribogaine itself did not possess significant antinociceptive activity alone, but did possess significant antinociceptive effect only when combined with morphine, an opioid agonist**. Thus, Bagal *teaches* away from the present invention, which is directed to the use of noribogaine alone (i.e., without a co-administered opioid analgesic) or in combination with an opioid **antagonist** to reduce or eliminate pain in a patient. In contrast, one of ordinary skill, reviewing Bagel, would conclude that, *at best,* the administration of noribogaine may be used in combination with morphine to provide significant antinociception activity, but that noribogaine *itself* was not a viable analgesic without such coadministration. Moreover, because the art recognized that opioid antagonists did not possess appreciable analgesic activity and morphine was an extremely potent opioid analgesic, a combination of noribogaine and an opioid antagonist is clearly not taught. In fact, one would conclude that noribogaine and an opioid antagonist should not even work, because such a combination would actually ***destroy or inhibit*** the antinociceptive effects of noribogaine and morphine. In essence, the Bagal teaching completely contradicts the present invention.

Thus, Bagal does absolutely nothing to obviate the deficiencies of Epstein, GB '697 or

Hussain. Indeed, if one of ordinary skill could draw any conclusions from Bagal, it is that noribogaine alone should not even work in the present invention, and that if noribogaine was to be used in an analgesic application, it only would be in combination with morphine, a potent opioid analgesic. However, that is not the present invention and Applicant has specifically disclaimed such a combination. In contrast to the teachings of the art, Applicant has discovered that not only does noribogaine work alone (a concept which is clearly contravened by the conclusions reached by Bagal), but that noribogaine is also effective as an analgesic in combination with an opioid *antagonist*, a concept which is contravened by the requirement of Bagal that morphine, a potent opioid agonist, is required to be used in combination with noribogaine. Thus, the present invention, with respect to the combination of noribogaine and an opioid antagonist, completely contradicts the teachings of the art precisely at the point of invention. Consequently, the present invention is non-obvious.

Based upon the teachings of Bagal and the only reasonable conclusions to be gleaned from that reference by the routineer, Applicant respectfully submits that Bagal actually *teaches away* from the present invention, in the first instance by suggesting that noribogaine cannot be used alone as an analgesic and in the second instance by suggesting that noribogaine can be effective when combined with morphine, a potent opioid agonist, not an opioid *antagonist* as is claimed by at least one aspect of the present invention.

The Examiner contends that Applicant did not provide sufficient clarity with respect to the patentability of the present invention over the combination of references cited. However, Applicant respectfully submitted and reiterates that a combination of the teachings of the references cited against the instant application does not render the present invention obvious. Either the references are devoid of any teaching of noribogaine, or where noribogaine is disclosed, those references actually teach that the present invention is not a viable approach or should be used in combination with morphine (opioid analgesia), an approach the instant invention clearly *avoids*. Consequently, because the art is wholly deficient and completely fails to teach or suggest the present invention, Applicant respectfully submits that the present invention is patentable.

Notwithstanding the deficiencies of the art, the Examiner posits in the office action Bagal discloses that noribogaine is an active metabolite, that disclosure can be used to support

the view that the present invention is unpatentable. Applicant disagrees. What Bagal posits (and what the routineer may glean from Bagal) is that noribogaine may be at least partially responsible for the activity ibogaine exhibits in enhancing morphine antinociception. Thus, Bagal perhaps suggests that noribogaine may be used to substitute for ibogaine in being combined with morphine. Bagal, however, does not suggest noribogaine itself possesses outstanding antinociceptive activity and may be used *alone, or in combination with an opioid antagonist* to treat pain. It is respectfully submitted, that Bagel clearly does not teach that noribogaine is useful as a "stand-alone" analgesic, but rather that noribogaine may be an effective agent *when combined with morphine, an opioid agonist*. A review of the amended claims evidences that Applicant has avoided any possible interpretation that claims read on that approach (a combination of noribogaine with an opioid agonist) by disclaiming a combination of noribogaine with an additive opioid analgesic agent such as morphine.

Additionally, the Examiner has relied on the fact that because Bagal disclosed that noribogaine is an active metabolite of ibogaine, one of ordinary skill would recognize that noribogaine could be used in the same manner as ibogaine to alleviate pain. Indeed, Applicant concedes that Bagal teaches that noribogaine can be used to replace ibogaine in combination with an opioid analgesic such as morphine. However, there is no teaching or suggestion that because noribogaine is an active metabolite of ibogaine, it can be used *alone or in combination with an opioid antagonist* as claimed. It is noted here that ibogaine has not been posited for use as an analgesic agent *alone*, in the first instance because it has virtually no activity as an analgesic agent (see, GB '695, which clearly indicates at page 2, column 1, lines 5-6 that the art recognized that ibogaine *per se* did not have analgesic activity) and in the second instance because it exhibits substantial psychotrophic side effects, thus negating its use a stand-alone analgesic (even assuming it had the requisite activity). Consequently, the fact that ibogaine is taught by Bagal for use in combination with an addictive opioid agonist such as morphine does not allow one of ordinary skill to make the inventive leap that noribogaine can be used *alone or in combination with an opioid antagonist* for the treatment of pain.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Applicants have not added or cancelled any of the previously presented claims in this paper. Applicants previously have cancelled 15 claims (two independent) in the present application. No fee is therefore due for the presentation of this amendment. A petition for a three month extension of time is enclosed as is the appropriate fee of $490 (small entity status applies). If any additional fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838. Should the Examiner wish to discuss the present application in an effort to advance its prosecution, the undersigned attorney may be reached at the telephone number set forth hereinbelow.

Respectfully submitted,
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